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INVESTIGATION OF CYCLIC LIGANDS INHIBITING CD2-CD58 INTERACTIONS USING MOLECULAR DYNAMICS AND MOLECULAR DOCKING APPROACHES

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The CD2-CD58 protein-protein interaction is known to favor the recognition of antigen presenting cells by T cells. Molecular Dynamics (MD) and molecular docking calculations are carried out to study the structural, energetics, and dynamical properties of three known cyclic CD58 ligands, named P6 [1-3], P7 [1,4], and RTD-c [3]. Each ligand, connected via turn inducers, mimics the C and F β-strands of protein CD2. The MD analyses focus on the location of the ligands on the surface of CD58 and on the direct and water-mediated hydrogen bonds (Hbonds) they form with that receptor. Ligand P6, with a sequence close to the experimental β-strands of CD2, presents characteristics that explain its higher experimental affinity, e.g., the lower mobility and flexibility at the CD58 surface, and the larger number and occurrence frequency of ligand-CD58 Hbonds. For the two other ligands, the structural modifications lead to changes in the binding pattern with CD58 and its dynamics. In parallel, a large set of molecular docking calculations, carried out with various search spaces and docking algorithms, are compared to provide a consensus view of the preferred ligand binding modes. The analysis of the ligand side chain locations yields results that are consistent with the CD2-CD58 crystal structure and suggest various binding modes of the experimentally identified hot spot of the ligands, i.e., Tyr86. P6 is shown to form a number of contacts that are also present in the experimental CD2-CD58 structure.

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References

1) Gokhale A, Weldeghiorghis ThK, Taneja V, Satyanarayanajois D (2011) Conformationally constrained peptides from CD2 to modulate protein-protein interactions between CD2 and CD58. J Med Chem 54:5307-5319
2) Gokhale A, Kanthala S, Latendresse J, Taneja V, Satyanarayana SD (2013) Immunosuppression by co-stimulatory molecules: Inhibition of CD2-CD48/CD58 interaction by peptides from CD2 to suppress progression of collagen-induced arthritis in mice. Chem Biol Drug Des 82:106-118
3) Sable R, Durek T, Taneja V, Craik DJ, Pallerla S, Gauthier T, Jois S (2016) Constrained cyclic peptides as immunomodulatory inhibitors of the CD2:CD58 protein-protein interaction. ACS Chem Biol 11:2366-2374
4) Gokhale AS, Sable R, Walker JD, McLaughlin L, Kousoulas KG, Satyanarayana SD (2015) Inhibition of cell adhesion and immune responses in the mouse model of collagen-induced arthritis with a peptidomimetic that blocks CD2-CD58 interface interactions. Biopolymers 104:733-742